

Is anti-factor Xa activity important?

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Is anti-factor Xa activity important?

To the Editor:

The elegant experiments of Cadroy et al.¹ have incited an editorial by Lane and Ryan² that concludes that anti-factor Xa activity seems a better yardstick of the heparin effect than antithrombin action is. This is in apparent contradiction to recent work³ (and references therein) that shows that in clotting plasma with heparin, (1) the anti-IIa action is the main cause of the diminution of active thrombin and (2) the free factor Xa levels can be inhibited over 60% without inhibition of prothrombin activation. This itself is in accordance with observations (cited in Cadroy et al.¹) showing that inhibition of factor Xa activity (pentasaccharide) has a poor antithrombotic effect compared with inhibition of thrombin activity (hirudin, dermatan sulfate).

The contradiction probably arises from the fact that the anti-factor Xa and the anti-factor IIa activities as given by Cadroy et al. bear no direct relationship to the activities of their samples. The anti-factor Xa values have been obtained with bovine factor Xa in the absence of Ca^{++} , whereas the relevant data are on primate factor Xa in the presence of Ca^{++} . The anti-factor IIa values given are measured by clotting tests that are either not specific (activated partial thromboplastin time [APTT]) or are notoriously imprecise (thrombin clotting time [TCT]).

We determined the increase, per microgram of heparin per milliliter, of the decay constant of endogenous human thrombin and factor Xa in human plasma. We also determined what part of the heparin would be bound to antithrombin III (ATIII) and what amount would be neutralized due to platelet factor 4 (pf4) that is released in clotting platelet-rich plasma from thrombin-activated platelets.^{3,4} With these data we calculated what the effect of the heparin concentration that causes 50% inhibition of thrombus formation (IC50) from Cadroy's experiments would be in clotting human platelet-rich plasma in terms of (1) available ATIII binding material, (2) the breakdown constant of factor IIa, and (3) the breakdown constant of factor Xa. The results are presented in Table I.

The argument of Lane and Ryan² is essentially that the ratio of unfractionated heparin (UFH) activity to low molecular weight heparin (CY222) activity is near unity when the concentrations are expressed in anti-Xa units, but not otherwise. When calculated on the basis of exact

Table I

	UFH	CY222	Ratio
IC50 from Cadroy (μg/ml)	6.25	33	0.2
IC50 in anti-Xa units	1	1.4	0.7
IC50 in anti-IIa units	1	0.15	6.7
Specific decay constant IIa (min ⁻¹ /μg/ml)	13	0.9	
Specific decay constant XA (min ⁻¹ /μg/ml)	6	0.8	
Amount not neutralized by pf4 (μg/ml)	4.25	31	
% Binding to ATIII	36	10	
IC50 of ATIII binding hep. (μg/ml)	2.25	3.3	0.7
Decay constant at IC50 (min ⁻¹) IIa	55	28	2
Xa	26	25	1

UFH, Unfractionated heparin; CY222, low molecular weight heparin; pf4, platelet factor 4; ATIII, antithrombin III, hep, heparin.

data obtained in human plasma—which might be a better approximation to what must have happened in the baboons—the choice between the possible modes of expressing the activity becomes much less obvious.

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